"The Social Life of 'Scaffolds': Examining human rights in regenerative medicine"

Abstract

Technologies for enhancement of the human body historically have taken the form of an apparatus: a technological device inserted in, or appended to, the human body. The margins of these devices were clearly discernible and materially circumscribed allowing the distinction between the corporeality of the human body and the "machine" to remain both ontologically and materially secure. This dualism has performed some important work for human rights theorists, regulators and policy makers: enabling each to imagine they can establish where the human ends and the other begins. New regenerative products such as *Infuse™* and *Amplify*™ subsist as animal-derived scaffolds seeded with growth hormone implanted within a prosthetic device. They are much more materially complex and their identities thus remain open to contestation. Following Jain (2006), I thus attend closely to their social lives, particularly the stories that are told about them and how these are employed to construct understandings of what kind of a phenomenon they are: systemic drug, biologic, or combinatorial medical device. The significance of this classificatory project is revealed in the final section of this paper, which explores how these stories shape understandings of "product failure," liability and causation when such products overflow their material and ontological categorization and their recipients become disturbingly "more-than-human."

Introduction

Regenerative medicine, "the process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal function" (Mason and Dunnill, 2008:4), has become a focus of increased public interest and scholarly research since the turn of the millennium. In social scientific circles, much attention has been devoted to analysing the highly politicized and contested acquisition of embryonic stem cells and the social and ethical complexities that attend their applied use as clinical therapies (Gottweis *et al*. 2009; Lo and Parham 2009; Robertson 2010). To date, despite some notable exceptions (Sobchack 2006; Besmer 2012), less attention has been given to examining the development and application of more materially diverse regenerative assemblages, or to exploring how their application might complicate notions of what constitutes "the human" or distort the practice of protecting something presently understood as "human rights."

Much of the debate that has emerged around regenerative devices has focused on their implications for realizing the "post-human." The line between restoration of function and enhancement can be very finely drawn and much has been made of the potential that such devices have for generating new renderings of the human: hybridized subjects of technoscience that resist essentialist characterization as either organism or machine (Oudshoorn 2015). Their reception has been mixed, to be sure. Most of the populist discussion of post-humanism has become highly polarized, dividing into one of two modalities: the hyperbolic and the apocalyptic, each of which vies for ascendancy in the public imagination (Lorimer 2009). The hyperbolic is essentially celebratory and optimistic, embracing technoscientific advances for their ability to create new post-human entities, the enhanced capacity of which will triumphantly, and unproblematically, exceed humanity's inherently limited "natural" potential (e.g. Harris 2011).

The “apocalyptic” reading of post-humanism provides a counterpoint to this view. Its advocates, such as Fukuyama (2002), also diagnose the arrival of a new epoch, however this is one considered fraught with danger. Here, technoscientific interventions threaten to pollute an essential (and essentialized) humanism, one sedimented in an earlier hermitically sealed and nostalgically revered ontological realm in which “humans were humans and nature natural” (Lorimer 2009:348). In more recent, nuanced readings the purported distinctiveness of the human, that is, its ontological separation from other entities, is challenged; the human is decentered from its privileged position and understood merely as an interlocutor in a wider conversation, “a space of becoming” that is shaped through complex encounters and entanglements with other species, technologies, discourses and practices. The human, as Whatmore reminds us is “no less a subject of ongoing co-fabrication than any other socio-material assemblage” (Whatmore 2006: 603).

In this “more-than-human” world of complex socio-material assemblages, materiality matters not because it provides an imagined determinant of what is and is no longer human, but rather because it reminds us of how the relationality of bodies, things, objects and arrangements creates new political ecologies, and new ways of framing and addressing particular sociotechnical problems (Gruen 2009). The concept of “fusion,” as both a dynamic and a register of materiality, can be helpful in pointing up how significant imbrication (of corporeality, technology and discourse) has become to the production and narration of various technoscientific artifacts (including humans). Even so, this is frequently effectively disavowed. Complex metrological work is often required to maintain the fiction that these elements remain distinct from one another. Legal regulation plays an exceptionally important role in the performance of this “boundary work,” generating and policing ontological jurisdictions through the application of mechanisms and discourses that allow protagonists to, theoretically at least, discriminate between one thing and another and thus, “adjudicate analytical controversies” (Lezaun 2012:22)

The discourse of human rights and the edifice of human rights law has undertaken precisely this kind of disciplinary work in its construction of the legal human subject: one broadly conceptualized, following the liberal tradition, as “a discrete individual with a singular identity characterised by rationality, uniqueness and *physical boundedness*” (Vaisman 2014: 395, my italics). Vaisman and other legal scholars such as Nedelsky have taken issue with the narrowness of such readings, arguing that the “legal person is always much more relational and intertwined with others than current legal instruments would have us believe” (Vaisman 2014: 395). Echoing Latour’s diagnosis that in a technoscientific world subjectivity no longer lives “inside, in the cellar of the soul but outside in the dappled world” (Latour 2002: 140), Nedelsky argues that human beings are in fact constantly coproduced through their relations with the wider world and that “their rights as well as their core attributes … are always part of, and created through, those relations” (Nedelsky 2011:38).

Both Nedelsky and Vaisman offer compelling examples of how conceptions of the legal subject as a bounded autonomous individual with a distinct personal identity and property rights are complicated and destabilized by the porosity of the human body, for example in attempts to distinguish between maternal and foetal tissue or when establishing rights to shed DNA (see the introduction to this special issue). For Vaisman, corporeal traces like shed DNA read like napped velvet: in one light they are constructed as the private property of the individual from whom they derive; in another, as evidential objects or “bodies of evidence” to which the Court can rightfully demand access. The rendering of the human as a socio-material narration rather than a fixed entity, is elegantly highlighted by these important contributions. The primary work of such studies is to examine how new technologies can trouble conceptions of the boundaries of the human legal subject and his or her rights. In these cases however, the body, although increasingly “leaky,” remains inherently human. My aim in this paper is to further such analyses by examining how

humans *themselves* are being materially refigured through the application of regenerative medicine in ways that compromise the subject's right to protection in law.

I take as my illustrative example a particular kind of regenerative assembly: engineered extracellular matrices. These "scaffolds," as they are known, have become key technologies in bodily repair and regeneration. The function of the scaffold is to act as an artificial structure that can be inserted into the body to support three dimensional tissue reconstruction. They are characterized in the wider literature as "medical devices." However, as I will argue here, they differ from their historical antecedents in some vitally important respects.[1] I focus on scaffolds for two reasons: the first is that they are constructed from an extraordinarily diverse amalgam of substances and materials including animal-derived collagens, carbon nanofibers, human growth hormones, synthetic polymers, metals, ceramics and other engineered biomaterials. The second relates to their mechanism of action. As I shall argue, restoration of bodily function has traditionally relied on the use of prostheses, devices whose material boundaries are tightly circumscribed. Scaffolds, however, are intended to operate very differently. They are designed to be fully adsorbed into the fabric and function of the body in ways that effectively collapse any meaningful distinctions between the corporeal, animal and technological elements of the renewed entity. My aim in this paper is to consider the implications that these developments have for the ways in which we conceptualize "the human" and its distinctiveness—from other species, forms of nature and technologies—but also, and perhaps more significantly, how this in turn shapes understandings of "product failure," liability and compensation in human rights law.

This then, is a paper of three parts: in the first, I briefly consider the history of technologies for bodily repair, paying particular attention to their constitution and mode of bodily incorporation; in the second, I compare the nature and action of more recent regenerative assemblages, including engineered organs such as decellularized porcine hearts reseeded with autologous stem cells, and cell-material hybrids that seed stem cells or growth hormones onto synthetic polymer scaffolds. In so doing, I pose a series of questions about how these entities are characterized in technical and regulatory terms. My aim is to explicate the social life of these scaffolds: to consider how their identities are constructed and maintained, by whom and for what purposes. Following Løchlann Jain (2006), I attend to the stories that are told about the nature of these scaffolds and their actions and consider how they construct understandings of what kind of a phenomenon they are: systemic drug, biologic, combinatorial medical device or engineered human tissue. I then explore the work that these constructed narratives perform in positioning these devises in regulatory terms and the implications this has for the subjects in which they ultimately diffuse. The significance of this classificatory project is revealed in the final section of the paper. Through a case study of two such devices, I explore what happens when they begin to overflow or exceed their material and ontological categorizations, and how this dynamic of *excess* comes to inform understandings of liability and causation when such products fail and their recipients become disturbingly '"more-than-human."

The Device as Apparatus

One of the central axioms of accounts of post-humanism, be they apocalyptic or hyperbolic, is that it is possible to identify a time—a retrievable historical moment—when the purity of the ontological realms of the human, the animal and the technological was assured, a time in which we could discern with confidence where the human ended and the animal or machine began. Taking this presumption as a point of departure (and a provocation), I begin by examining something of the history of bodily repair and enhancement. Focusing primarily on mechanical devices, my aim is to

[1] See O'Brien, 2011 for a more detailed summation of their structure and action.

examine how their constitution, application and operation have changed over time. I do so in order to assess the implications of the most recent advances for the way in which we conceptualize what a "device" is, and consequently of where any boundary between it and the human might conceivably lie, or, be meaningfully discerned. The political and social status of the human as a fused "assemblage" has long preoccupied social commentators, and yet to date we have closely examined few real life examples. Here we have an opportunity to explore how a politics and praxis of "excess" can emerge: to consider what occurs (both legally and ethically) when devices begin to escape the conceptual and operational parameters imagined for them and come to fully inhabit the human in unpredictable ways.

William Gibson's 1984 work Neuromancer provided an extraordinarily potent evocation of a futuristic figure, the cyborg: a molten construct of prosthetic limbs, implanted circuitry, artificial intelligence and super human capabilities. Humans, in this sci-fi account become thoroughly engineered entities capable of being not only repaired but also enhanced technologically. How though to situate this figure within the long durée of attempts to reconstitute or augment bodily capacity? A glimpse into history provides some significant precursors that suggest points of both similarity and departure. There have been many attempts to draw lines of distinction between those technologies that restore function or compensate for deficiencies and those whose usage allows the recipient to gain enhanced capabilities. Early examples of such technologies include the wooden and leather toe recently unearthed from the Egyptian tomb of a female mummy[2] (Finch *et al.* 2012), whose purpose, like many other such devices was to enhance functional mobility. Visual enhancement technologies have a similar history and action (Ilardi, 2004). From the 17th century onwards such devices become infinitely more elegant and mechanically sophisticated (c.f. late Victorian steel and brass artificial hands), but also transformed from being simply attachable to insertable: Hansman's bone repair plates for example. By the late 19thcentury new terminology had been introduced to describe these technologies: *prostheses*, derived from the Greek meaning an "addition, application or attachment in place," now defined as "a device, either external or implanted that substitutes for or supplements a missing or defective part of the body."[3]

Since then our propensity and ability to re-engineer our failing bodies has advanced exponentially, driven in part by the demographics of rapidly ageing populations in the West, and State support for interventions that reduce the costs of aged care and generate income through innovation. Uptake is evidenced in our eager adoption of everything from replacement hip and knee joints and artificial corneas, to equipment such as the Jarvik artificial heart. What unifies all of these devices (whether conceptualized as tools of repair or enhancement) is that they have historically taken the form of *an apparatus* in both senses of the word: as both a piece of technical equipment or machinery (an object) and a framework for operation (a system) that is *materially circumscribed*.

By this I mean that the technical margins or boundaries of these appliances and their mode of operation or action are discernible and limited, allowing the distinction between the corporeality of the human body and the "machine" to remain both ontologically and materially secure. This has important implications for both product operation and failure. Let's take, for example, a device such as the Jarvik heart. Although sutured into the body there remains a clear distinction between the unforgiving rigidity of its titanium and tubing and the malleable pulpy flesh in which it's embedded: it is not difficult to determine where the human ends and the technology begins. The device as object lends itself to technical inspection and relatively easy retrieval. As we shall see, the same cannot be said of the devices that are the subject of this paper.

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[2] http://www.bbc.co.uk/news/education-19802539

[3] Oxford English Dictionary citation for first modern use of prosthetics in 1894; Word Reference Dictionary Random House Unabridged Dictionary of American English, Random House New York, 2017 for the current definition.

In the interest of complicating this argument we might consider the action of some other technologies of bodily repair. Medicines, drugs and vaccines could all be characterized as such, however they are presumed from the outset to be suffusive in action and are thus not characterized as devices *per se*. Other historical examples of regenerative technologies that were designed to permeate or were meaningfully melded into, or with, the body in ways that made them effectively indistinguishable from each other exist, but are less commonplace. In the early 19th century, so-called Waterloo Teeth were extracted from soldiers on the battlefield of that war and either implanted directly into the sockets of wealthy recipients or alternatively, fixed onto rudimentary dentures (Sproull 1978; Engelmeier 2003). Whilst the latter could be conceptualized as a device, the teeth were intended from the outset to be incorporated into the fabric of the recipients' bodies. They were, consequently, simply an early example of transplantation of bodily material from one human to another.

The dissolution of distinctions between the corporeality and subjectivity of *humans and animals* had begun several centuries earlier with the development of new perfusive technologies of bodily regeneration. From the late 17th century onwards natural philosophers began to devise new techniques for transfusing the moribund with the blood of animals, including lambs. This was not because that blood was viewed as literally worth less but rather because it was believed to have been less likely *"… to be rendered impure by passion or vice."* [4] Whilst we might imagine that such experiments were viewed as disturbingly transgressive given their capacity to de-stabilize previously secure ontological distinctions between the human and the animal, they were often embraced as being uniquely restorative. Commenting on just such an experiment in 1705, Purmann[5] remarked that the change that ensued in the patient was *"startling,"* with the boy showing *"… a clear smiling countenance,"* where previously he had apparently passed the time *"… in an incredible stupidity."* There was much speculation at this time about the value of blood exchange between species; it had been suggested, for example, that blood from a gentle lamb might quiet the tempestuous spirit of an agitated person and that the shy might be made outgoing by blood from more sociable creatures. However, attempts by physicians to transfuse animal blood into humans generally gave variable and often fatal results due in part to allergic reactions, and such experiments were later abandoned. The xenotransplantation of animal organs to human recipients sustains this tradition but its success has been similarly compromised by the risk of xenozoonosis, permanent alterations of genetic code, and inherent differences in the respective life spans of the species.

At this point in the history of bodily regeneration we have essentially three kinds of available technologies: those that are meant to suffuse the body but whose actions are usually temporally limited and reversible (e.g., drugs); forms of corporeal transplantation (whether intra or inter species) that involve blood or tissue exchange but not the insertion of mechanisms; and object mechanisms/devices (such as prosthetic legs or hearts) that are designed to be inserted in or appended to the individual but not perfuse within them. These distinctions have become the basis of contemporary systems of regulatory classification for their use. The underpinning presumption is that distinctions between the corporeality of the human body, animals, and technology will remain for all intents and purposes, ontologically and materially secure. This is, however, no longer the case.

[4] The first transfusion of this kind was performed by Jean-Baptiste Denis in Paris in 1667, who noted that he preferred to use animal (rather than human) blood, as he believed it less likely "to be rendered impure by passion or vice" (Cited in Shaz 2013).

[5] "Sheep to Man" (Purmann 1705, cited in Moore 2003).

Entirely new kinds of regenerative assemblages have since emerged that thoroughly complicate such distinctions by collapsing the boundaries between the device, its constituent parts, and the human in which it is placed. These technologies exceed existing categorizations in a number of ways: they are complex entities that are multiply constituted from amalgams of human and animal tissues, natural and synthetic materials. They are insertable objects but they are not inert. Their application within humans changes the latter's constitution in very significant ways that are not temporally limited. The simplest definitions characterize a cyborg (Haraway 1991) as an entity that is "part human part machine." However, this reading fails to capture the liveliness of the dynamics now at play. Simply adding mechanical modifications doesn't turn a human being into a cyborg. For that to occur there must be an ongoing iterative engagement with the device. In short, these mechanical modifications must be linked to or directed by some kind of feedback response from the organisms itself. Neither "object devices" (such as wooden legs) nor human body parts (such as the Waterloo teeth) has had this kind of relationship to the bodies in which they were inserted. More contemporary devices such as hip replacements are encouraged to interface with the surrounding tissue, whilst thought-directed prosthetics may both "listen to" and "talk back" to the body. Neither, however, has demonstrated the kind of agency acquired by the regenerative assemblages under scrutiny here. These devices are not simply in dialogue with their recipients; they have come to take on lives of their own.

The Device as Lively Assemblage

In what ways does the vibrancy of matter—matter? This question, posed by Jane Bennett in her monograph, *Vibrant Matter* (2011) animates much of the following analysis. As she notes therein, the philosophical project of naming where subjectivity begins and ends "is too often bound up with fantasies of a human uniqueness in the eyes of God, of escape from materiality, or of mastery of nature" (2011: ix). Neglect of the political agency of materials, that is to say the capacity of apparently inert objects to shape encounters and to produce profoundly inequitable outcomes, is certainly prevalent. However, as Bennett and others demonstrate, the significance of materiality can be redeemed by paying closer attention to its inherent vitality, what Bennett (2011: xvi) describes as "the strange ability of ordinary manmade items to exceed their status as objects and to manifest traces of independence or aliveness, constituting the outside of our own experience." In this section I thus draw attention to the emergence of a new collective of regenerative devices that are not only materially diverse but lively. By lively I mean, devices that have forces, propensities and tendencies of their own, that exist not as inert "things" but rather as active participants, interlocutors, if you like, in a wider conversation about what the being they are inserted into, is, or could become. In fact, as we shall see, their agency is such that they have begun to operate autonomously within the recipient body, escaping to colonize them in ways that complicate and exceed all the binaries on which their existence is premised.

The world of regenerative medicine and the nature of the assemblages with which it is populated are immensely complex and undergoing rapid and continual change and innovation. Demand for devices is rising exponentially, driven by global ageing and the desire of many to reengineer their ailing bodies. Pharmaceutical, biotechnology and medical device companies now invest more than 60 billion US dollars per year on research and development worldwide with many hundreds of thousands of devices approved for use each year (Pashuck and Stevens 2012:1). Discussing each is clearly beyond the scope of this paper, but it is important to note that paradigmatic shifts are occurring in the manufacture of such devices that have serious implications for classification and regulation. This is because these new assemblages have the capacity, in terms of both their constitution and mode of operation, to trouble, if not completely undermine, conceptions of the uniqueness of the human and inviolability of the human body on which so much of human rights and medical law depends for its intellectual purchase and legal application. As space is limited I focus here on just one such device, though with a brief introduction to others of its kind.

Assistive *medical devices* take many different forms: some remain entirely external to the body (splints, blood glucose monitoring kits); others such as contact lens or ultrasound scanners are minimally invasive; pacemakers are insertable, and titanium joints b implantable. Whilst the latter are designed to be embedded into surrounding bone, they remain essentially objects, the material boundaries of which remain both distinct and discernible. They are employed on or in the body but are designed to become only minimally imbricated in its fabric. In this respect they differ significantly from *medical products,* including small molecule drugs that are designed to work systemically. Relevant authorities, including the European Commission (through its Medical Device Directives) and the Food and Drug Administration (FDA) in the US, are responsible for regulating not only medical devices but also these more lively commodities: drugs, therapeutic proteins and antibodies, biologics including viruses, toxins, vaccines and blood components, and additionally cells, tissues, gene vectors, and tissue engineered products.

Such authorities typically order regulation of devices by reference to perceived risk to the recipient. So, for example, under the FDA system elastic bandages are classified as Class I (low risk); acupuncture needles as Class II, with Class III reserved for those devices such as pacemakers "that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury."[6] The key distinction between drugs and devices has always been constructed by reference to their materiality and their modes of action. Medicinal products or pharmaceuticals are considered to act by pharmacological, metabolic or immunological means—through diffusion *within* the body; medical devices by physical, mechanical, or thermal action *upon* the body.

These comfortable distinctions between drugs and devices have been seriously complicated by the emergence of a new kind of entity described by the industry as "Combinatorial Products." As the name suggests they herald a complete change in approaches to tissue engineering, as they are multiply constituted and perform their work in complex, over-determined ways. Given that a primary goal of regenerative medicine is to renew organs and tissues, it is unsurprising that scientists have focused on harnessing and amplifying the vital restorative capacity of cellular material itself. Cellular activities such as quiescence, growth and differentiation that are central to tissue repair and wound healing are organized via cell signalling mechanisms in the extracellular matrix (ECM)—the material that surrounds and sits between cells. With recent advances in bioengineering it has become possible to manufacture novel ECMs from either naturally occurring or synthetic biomaterials. These include collagen derived from human bovine and porcine organs, polymer scaffolds and matrices, nonwoven fabrics and woven surgical meshes. Some scaffolds are made from collagen that is de-cellularized (that is to say, stripped of all its existing cellular material) to create an organic, protein rich, but inert disinfected structure such as Doris Taylor's ghost heart (see Maher 2013). Denuded of its original cellular tissue, this spectral apparition of an organ waits only to be repopulated with cells from a potential recipient in whom it can be transplanted without risk of rejection.

The scaffold then can be seen as an anchor point, a mechanical structure to which cells can adhere, and then proliferate and produce new tissue. In this sense, they may seem to conform to the definition of a "device." However, the cell interactions that promote growth can be mimicked—indeed, functionally enhanced—if the scaffold is made to serve not just as a simple architecture but rather as a therapeutic entity in its own right. This can be achieved by seeding the ECM with bone morphogenetic proteins, small molecule drugs, nucleic acids, or growth factors derived from human and animal sources. These are used to promote cell proliferation, differentiation, migration, motility and adhesion, all key to tissue development and repair. These amalgams of synthetic and natural

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6 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/default.htm.

materials, and human and animal tissues coexist in varying states of vitality and operate through diverse modes of action. Scaffolds are often held in place by an old fashioned "mechanism" designed to be bolted in to the wound site; the scaffold itself will become incorporated into surrounding tissue over time, whilst the proteins and growth hormones it contains are intended to suffuse the local area to promote tissue repair. They are designed to be both constitutively dynamic and responsive to bio-feedback, becoming, consequently, essentially cybernetic in their action. These new assemblages have thus become lively, and, unsurprisingly in my view, are disinclined to "sit still" either materially or ontologically. This creates huge regulatory complexities, although these are frequently disavowed.

Devices, for example, are defined by the FDA as something which "does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and is not dependent on being metabolised …"[7] However, as Whittaker *et al.* (2001:1433) have argued, many current technologies in this field, particularly those that seed growth hormones into insertable scaffolds, "have borrowed from conventional concepts of controlled release of small drug molecules" in that their action is intended to be systemic. Moreover, these assemblages transgress one of the key defining characteristics of a device that is relied upon to distinguish them from other medicinal products such as pharmaceuticals—that they be "materially circumscribed in their constitution or action." Many scaffolds are, conversely, now designed to *diffuse*. They are intended to be either biodegradable within the body (such as collagen that can be actively degraded by cells) or to merge with the body over time. As Whittacker *et al.* note (2001: 1428) this should technically allow for natural long-term replacement of the tissue without the complications associated with "foreign" implants. This brings us, however, to the nub of the matter and one of the most poorly understood and theorized questions in this field: what exactly now constitutes a "foreign body" in regenerative medicine? What implications does not being able to establish where the "foreign" body ends and the "native" body begins have for regulation, and ultimately for the protection of individuals whose corporeality is so fabricated?

The Social Life of Scaffolds

The task of arriving at strict or defensible definitions of "the human" and "the technological" is complicated by these advancements, which thoroughly blur the boundaries between older and seemingly more ontologically secure definitional categories: the natural and artificial; lively and inert; organic and manufactured. They are also rendered irrelevant in a world in which the interweaving of human and technology is considered not only inevitable but also welcome. However, as Van Den Ede argues (2015:159), although the figure of the "technologically mediated being-in-the-world" is already a taken for granted reality, negotiations and debates remain over the form and function that these hybrid entities might take. This has significant political implications, for, as he notes, "even if our human being is built on shifting sands, decisions still need to be made about how this edifice should evolve, *architecturally*." Architecture is a useful term here as these technologies are designed to fundamentally alter the habitus of human existence. This is achieved through the application of manufactured products, such as scaffolds, that have utility but also the potential for risk and damage. As such they become a subject in themselves—the subject of legal regulation.

As Løchlann Jain argues in her groundbreaking work *Injury*, law-making performs vital cultural and political work in establishing the ontology of such objects. It does so by stabilizing narratives about the "agreed nature" of such things. Law here provides a discourse "through which the fluidity of everyday interactions is stilled" (2006:5). These narratives are potent as they are later translated into norms relied on in court to render intelligible the artifact-body interface and to adjudicate

[7] http://www.fda.gov/RegulatoryInformation/Guidances/ucm259059.htm

where responsibility lies when things go wrong. For these reasons, and in this case, it is therefore important to attend to the work that law is asked to perform in protecting human life, to the stories that are told about the nature of these new combinatorial products, and to how they construct understandings of what kind of a phenomenon they are: systemic drug, biologic, medical device or engineered human tissue. The work may appear to be mundanely classificatory, but is hugely politically significant as it acts to distribute risks to unsuspecting consumers in ways that profoundly compromise their human right to an appropriate "duty of care" and "quality of life."

Legal regulation of device manufacture, sale and use is an immensely complex and geographically differentiated field, one that cannot be fully discussed here. I can provide only a brief overview of how the lives of these scaffolds have been interpreted and narrated by one regulatory agency: America's Food and Drug Administration or FDA. Here I concentrate on revealing how specific readings of the material composition and action of these novel assemblages are deployed to legitimate their instantiation as a device rather than as a drug or biologic, and how this in turn conditions the fate of those who ultimately use them. The FDA has developed its regulations in relation to the protection of human subjects through reference to the Declaration of Helsinki, which is an instrument designed to protect the human rights of those who are involved in, or likely to be recipients of, experimental biomedical research.[8] Key amongst the principles thus adopted by the FDA are those demanding that: "concern for the interests of the subject must always prevail over the interests of science and society, that medical research involving human subjects conform to generally accepted scientific principles; be progressively evaluated and overseen by appropriate and independent review boards."[9] Of course, questions of what the referent in these regulations— "the human" -- actually is, or how it could conceivably be altered by the application of such technologies are never explicitly addressed in any subsequent FDA discussions or regulations that I have seen. The "human" is an entirely taken for granted ontological category—even as the "purity" of its existence is being progressively eroded by the clinical developments that such organizations promote. This is perhaps most evident in the FDA's approach to the regulation of new "combinatorial products."

One of the great difficulties that the FDA has faced is that of discerning how distinctions between drugs, biologics and devices can now be meaningfully established or maintained. As legal theorists have acknowledged, "difficult borderline questions arise in relation to a significant number of products particularly in relation to whether they are to be classified as medicinal products or as medical devices" (Grubb et al. 2010: 946). Narrative judgements on where such boundaries lie must be arrived at, however these have inevitably come to rely on subjective interpretations of key criteria. It might seem that it matters little what identity is ultimately narrated for these complex entities as long as that narration remains consistent. But the question of how they are classified proves to be a very significant one. This is because their ontological status—what they are understood or argued to be—goes on to set their pathway through the regulatory landscape,

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[8] Other International regulations and domestic reports that have also been adopted in part or in full to guide the protection of human subjects in medical device research by the FDA include: The Belmont Report (1979); The International Conference on Harmonisation (ICH-GCP); The International Standards Organization, Code 14155; and the US Code of Federal Regulations

[9] Historical records and more recent information available at the FDA website document and reflect the adoption of these principles. See:
http://www.fda.gov/downloads/scienceresearch/specialtopics/runningclinicaltrials/ucm521400.pdf

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=50&showfr=1

dramatically shaping how they are tested and later deployed in clinical practice. Their trajectory also has considerable financial implications for manufacturers as the time and costs required for approval are also highly pathway dependent. The key point to note here is that there are considerable commercial advantages to corporations in constructing a story that these complex scaffold assemblages remain primarily a device rather than a medicinal product. As Pashuck and Stevens (2012: 14) demonstrate, securing regulatory approval for a new pharmaceutical or biologic costs hundreds of millions of dollars and more than ten years of clinical trialling to secure. Obtaining pre-market approval for devices (even Class III) is considerably less onerous in both EU and US jurisdictions, typically taking less than five years and between 45 and 150 million USD to obtain.

This is because devices, so described, go through far less stringent testing and trialling procedures than do medicinal products. Why is this so? The materiality of the device lends itself to the construction of a story about its presumed mode of operation. As the device is assumed to operate in localized and mechanical ways, it is argued to have less probability of generating systemic effects in the ways that pharmaceuticals or biologics might. It is thus generally presumed that any negative reaction would typically be confined to the area around the device and would consequently be more easily detected in preclinical development and pose fewer risks in practice. It is also imagined that as the device is clearly circumscribed it will be easier to extract if it malfunctions. In order to demonstrate the insecurity of this line of argument, I turn now to an examination of how the social lives and identities of two combinatorial devices marketed by the industrial medical device giant Medtronic were framed within the FDA, and of what happened when the devices began to "go rogue". As I shall demonstrate, in so doing they came to exceed not only their intended sites and mode of action but also the boundary work that had been invested in attempting to contain them, both ontologically and categorically.

Infuse™ and Amplify™: The Praxis and Politics of "Excess"

Infuse™ is a combinatorial bone graft device approved by the US Federal Drug Administration in 2002. It is designed to enable spinal fusion in individuals suffering from chronic lower back pain due to lumbar disc erosion or collapse. Materially complex, it is constituted of a metal prosthesis (a hollow machined cylinder of titanium alloy) filled with recombinant human Bone Morphogenetic Protein (rhBMP-2 derived from a genetically engineered Chinese hamster ovary cell line). This is seeded into an absorbable bovine collagen sponge that acts as a degradable scaffold to induce de novo bone regeneration at the site. Another similar product from Medtronic, *Amplify* ™rhBMP-2 Matrix has a ceramic prosthesis and is seeded with BMP in even greater concentrations than that found in *Infuse™* (Carragee *et al*. 2011).

The regulatory pathway that a regenerative technology is sent down is largely determined by the product's mode of action. However, in combinatorial products it is not always possible to discern what this might be, especially if there are two or more *equally significant* therapeutic effects delivered through two or more *independent* modes of action. This was the case with the *Infuse* ™and *Amplify™* devices. The prosthesis acted as an important load-bearing device whilst the rhBMP laced collagen scaffold acted as a drug delivery apparatus that induced cell and bone growth. Where actions are combined in a single technology, determinations of what they are—a device or a medicinal product—have ultimately come to rest on which action is deemed ancillary to the other. The FDA acknowledged this reality in May, 2004, proposing that such technologies be assigned for evaluation to one their three regulatory agencies, the Center for Devices and Radiological Health (CDHR); Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) on the basis of what the FDA determined to be their "primary" mode of action (PMOA).[10]

[10] http://www.fda.gov/OHRMS/DOCKETS/98fr/05-16527.htm

This proposal sparked much consternation at Medtronic, as they quickly recognized that characterizing the PMOA of *Infuse* and *Amplify* as something more akin to a drug than a mechanical device would consign them to CDER rather than the CDHR for evaluation, a decision that would double review times and costs. In a memo to the FDA, Medtronic's Senior Regulatory Director, Winifred Wu reminded the FDA that the Agency had identified novel delivery technologies (such as seeded scaffolds and implantable neurostimulation devices) as priority areas for growth, agreeing to foster innovations by considering "the 'least burdensome' requirements in evaluating safety and effectiveness."[11] Arguing for more flexibility and a lighter touch in regulation of these technologies, Wu went on to note that revising definitions of primary mode of action could "fully redefine jurisdictions for [therapeutic] delivery systems." It would do so, she suggested, by undervaluing the importance of the delivery system itself (the device) and characterizing "the drug or biologic component as providing the most important therapeutic action."

Rejecting this course of action, she argued for the defense of the FDA's historical position: that the CDRH should retain lead jurisdiction in instances where "the delivery system is intended to deliver generic drugs, drugs with specifications that are well defined, 'grandfathered' drugs and other drugs for which the safety and efficacy have been established via decades of medical use." Medtronic's defense of this pathway was largely motivated by the success they had already achieved in securing approval for single devices or elements of combinatorial devices via such routes. In 2002, for example, they had successfully secured approval for both the *Infuse* and *Amplify* devices via a Pre-market Approval (PMA) Process undertaken by the CDHR rather than the CDER; albeit with a requirement to conduct an extensive post approval study to obtain six years of post-operative data from a representative sample of patients implanted with this device.[12] PMA approval of these assemblages as "devices" rather than as drugs or biologics had greatly facilitated their progress to market, hence Medtronic's interest in maintaining this particular narrative about their constitution and operation.

A key distinction between a medicinal product (drug) and device is that the latter must not "achieve its primary intended purposes through chemical action within or on the body … [nor be] dependent upon being metabolized for the achievement of any of its primary intended purposes." Despite the already well-established metabolic effects of growth hormones (Mauras *et al*. 1996), Medtronic were able to successfully argue their case, allowing both products to be narrated and regulated by the FDA as "devices."[13] In practice, these combinatorial products came to overflow that categorization, both materially and ontologically. The trademarks *Infuse™* and *Amplify™* proved to be rather uncannily prescient in this respect. The concentration of rhBMP-2 loaded into the absorbable collagen scaffold within the device proved to be, as Paschuk and Stevens (2012: 8) have noted, "a million times higher than physiological levels and many times higher than needed in nonhuman primates and mice." No longer fixed within the materially circumscribed confines of the prosthetic cage, this recombinant growth hormone began to circulate and suffuse well beyond the localized site of insertion invoking and amplifying the recipient's biological response until they became disturbingly "more-than-human." Their mode of action proved not to be primarily mechanical but rather fundamentally systemic. These powerful biologics came to inhabit the entire corporeal fabric of the body seeding it with new vitality and new abilities for molecular proliferation.

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[11] Wu.W. (2004) Memo to the FDA regarding establishment of the primary mode of action of combinatorial devices. Available at: http://www.fda.gov/ohrms/dockets/dailys/04/aug04/082404/04n-0194-c00007-vol1.pdf. Accessed on 12/11/2015.

[12] http://www.accessdata.fda.gov/cdrh_docs/pdf/P000058A.pdf

[13] http://www.fda.gov/ohrms/dockets/dailys/04/june04/060704/04m-0249-aav0001-02-approval-order-vol1.pdf#page=1&zoom=auto,-89,815

It did so in ways that superseded anything anticipated by its manufacturers creating, in the process, a very potent "politics of excess."

Some regulators were uneasy with the move to classify *Infuse™* as a device, voicing concerns at the first FDA panel hearings that its PMOA was inherently systemic, that its pharmacodynamics within the body were not well understood or containable, and could thus have life-threatening impacts when used in prescribed, but also in off-label uses such as in the cervical, rather than lumbar spine.[14] Although their objections were overridden, reports soon began to emerge of serious complications associated with the *Infuse™* assemblage and in 2008 the FDA itself issued a Public Health Notification of "life threatening" adverse events associated with its use".[15] These included "swelling of neck and throat tissues which resulted in compression of the airway; difficulties swallowing breathing or talking … [that required] intubation, anti-inflammatory medication and tracheotomy" (Carragee et al. 2011: 473). Even more alarming bodily responses began to be documented from 2008 onwards, including uncontrolled bone formation leading to massive protuberant bony outgrowths of the lower spine, neurological events, retrograde ejaculation, chronic pain, male sterility and paralysis (Epstein 2013). By 2012 Riew *et al.* (2012: 901) had confirmed perhaps the most catastrophic complications to date, with the FDA itself reporting that the higher doses of rhBMP-2 (40 mg) used in the *Amplify*™ device were associated with a sevenfold increase in cancer events in recipients only 30 months postoperatively.

Unsurprisingly, this has resulted in significant legal damage claims submitted by over 6,000 individuals adversely affected by product failure in multiple US courts[16] and in a class action by Medtronic's shareholders whose share value was compromised by the suppressed notification of more than 1,000 adverse events between 2006 and 2008 alone.[17] Whilst the recent payment of 22 million US dollars to an estimated 950 claimants[18] might appear to resolve the issue, a closer analysis reveals that the case obscures much more than it clarifies about the ways in which the boundaries between the human and the machine, the artificial and natural, the normal and pathological are constructed and tested and how human rights are ultimately delivered (or not) in such cases. In concluding this paper I want to turn lastly to address the fate of these "more-than- humans" to consider how their very "humanity" has been put to work in the prosecution and at times annulment of their claims.

Proving fault and causation in a "More-Than-Human" world

Medtronic's successful narration of the story that *Infuse*™ and *Amplify™* were devices whose primary mode of action was mechanical and localized, rather than distributed and pervasive, legitimated a decision by the FDA to have them evaluated via the less demanding CDER route. Evaluation of the performance of the device was intended to continue via post approval studies. As Carragee *et al.* (2011) has revealed in his wide-ranging review of these studies, from 2002 onwards results of small and large trials were increasingly reported. Crucially, all these trials were industry sponsored. The safety findings in each case were identical: none reported a single adverse effect

[14] https://www.documentcloud.org/documents/2779798-Jan-2002-FDA-Infuse-Panel-Transcript.html Page 17.
[15] http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062000.htm
[16] Dennis Brian Anders, Plaintiffs, et al. v. Medtronic, Inc., Medtronic Sofamor Danek USA, Inc., And Does 1 – 100 Defendants, case number No. 4:14cv01637 ERW, filed October 17, 2014 in the United States District Court Eastern District of Missouri Eastern Division is one prominent example.
[17] West Virginia Pipe Trades Health & Welfare Fund et al. v. Medtronic Inc et al., 8th U.S. Circuit Court of Appeals, No. 15-3468.
[18] http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=1927406

from use of rh-BMP-2 in *Infuse* and *Amplify* technologies. As he remarked, given that 780 patients received rh-BMP-2 in these trials and that not a single adverse event had been reported "the estimated risk of rh-BMP-2 could be calculated to be less than 0.5% with 99% certainty … less than one-fortieth of the risk of a course of commonly used anti-inflammatory or antibiotic medications" (2011: 470). The profoundly rapid uptake of the use of scaffolds seeded with rh-BMP-2 in spinal fusions (which rose from 0.7% of all fusions in 2002 to 25% by 2006, including an exponential increase in off-label use)[19] was undoubtedly driven by publication of these very favorable industry sponsored trials that reported no adverse effects from use of what Carragee *et al.* describe as "these powerful biologic products" (2011: 472).

How did those individuals "regenerated" through application of these new biologics live in and with their newly engineered humanity? For those adversely affected, the systemic toxicity of rh-BMP-2 has had what could only be described as utterly ruinous impacts on their everyday lived experience, leading to thoroughly blighted futures.[20] Extensive reports have documented the dire existence endured by such subjects,[21] including that of Tom Engel, a formerly healthy man now fully bedridden who survives only with the assistance of morphine delivered via an implanted pump (ironically also made by Medtronics) and a tracheotomy that prevents him from dying from respiratory collapse overnight.[22] This is not a singular account but rather mirrors those reported daily in many medical blogs and forums.[23] Studies undertaken at Yale (Simmonds *et al*. 2013) and Stanford Universities (Carraggee et al. 2011) have since confirmed a significantly larger incidence of cancer fatalities amongst such recipients. The 2014 award of compensatory payments to 950 adversely affected individuals seems positive; however they represent but a fraction of the one million plus recipients that Medtronics itself reports have received the Infuse device worldwide since 2002. Moreover, the payment, as Medtronics noted in a press release,[24] is not an admission of liability on the company's part, but rather should be seen to constitute "a compromise of disputed claims." The Company continues to support the product and intends to "vigorously defend" its use in forthcoming cases. On what grounds have the patients' claims been disputed and how have readings of human constitution and response been enrolled in Medtronic's rejection of their claims?

Liability, as Jain suggests, is very much a social construction, another powerful narration that seeks to invoke and standardize an idealized person, one in whom all differences in physical reactions to objects or technologies are erased. This performs the work of allowing injuries to be set out as "states of exception" rather than as part of a range of "normal" anticipated responses that will distribute risk differentially amongst populations. The cornerstone of public liability law in the US and elsewhere is that a manufacturer is strictly liable when a product it develops is placed on the market knowing that it will be used without inspection for defects, which then proves to have a defect that causes injury to a human being. However, concepts of the limits of normality and the

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[19] FDA approval was given only for a narrow range of spinal fusions. However, industry sponsored trials that reported no adverse effects prompted much wider "off-label" uses. As one surgeon reported "we have used it in ways that were not originally approved by the FDA because we felt, if it works so well for one indication why not try it for others? Many of us read early articles on off label use which showed the results were excellent." Cited in Caragree et al. 2011:473)

[20] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi__id=2892772 provides one personal account of an Infuse failure in an adverse event report to the FDA.

[21] http://www.latimes.com/business/la-fi-ucla-wang-medtronics-20160729-snap-story.html gives an account of the suffering endured by two successful claimants. Other reports come directly from representing lawyers: https://www.lawyersandsettlements.com/articles/medtronic-infuse-bone-graft/interview-medtronic-lawsuit-bone-graft-14-20215.html

[22] http://archive.jsonline.com/watchdog/watchdogreports/130054948.html

[23] http://pogoblog.typepad.com/pogo/2011/06/war-breaks-out-over-medtronics-infuse.html The comments following the post provides a good indication to the response such articles attract in blogs and forums.

[24] See Footnote 15 above.

pathological—of what is a normal or abnormal response—of what can be "humanly" accommodated are also highly individuated in law. In other words, as Jain argues (2006, 122) "the law requires each plaintiff to come to the law separately" and cases can be dismissed or liability and compensation limited precisely because only some individuals suffer these adverse events. Another story is here constructed about "human nature"—of where the margins of human corporeality and endurance lie. One person's successful enhancement is another's catastrophic complications.

In considering the fate of those who have either yet to succeed in their claims or who may in future claim against defects in similarly complex combinatorial products, it is important to understand the test of causation in the establishment of negligence. The process of establishing a definitive causal link between the purportedly defective product and injury or adverse effect becomes infinitely more difficult when the distinction between the materiality of the technology and the corporeality of the subject becomes technically indiscernible. Attribution of causation of elevated rates of cancer, sterility or paralysis is difficult to verify in most medical tort cases but can be improved when the damage is relationally proximate to the device. But when the adverse response is more diffuse and distributed (chronic pain for example), and when suffusion acts to mask or even completely obscure the relationship between the causal agent and the "site" of contamination, proving causation becomes problematic. Indeed, injury can be more easily attributed to an "excessive" bodily response, characterized and dismissed, for example, as a sustained "allergic reaction." Strict product liability laws were intended to relieve the injured consumer from the burdensome requirements of proving negligence. However, personal injury claims in relation to the clinical application of regenerative assemblages can prove very difficult for a claimant to win due to their inability to establish "beyond a reasonable doubt" that it was the therapy that caused their medical problems and not an already underlying condition or predisposition. As Grubb concludes (2013:980): "proof that design defects are attributable to negligence is often elusive but seldom more so than in the case of medical products."

Conclusion

Respect for the tenets of human rights law—including, centrally, the right of human subjects to be protected from the insults of injury and distress induced by exposure to unsatisfactorily regulated devices—underpins and animates much of the work of the Food and Drug Administration. Part of the agency's primary responsibility in delivering this goal is to adjudicate how devices, biologics and medicinal products interface with the human. The progressive normalization of the "hard engineering" of our species through the application of a host of regenerative products drives the expansion of lucrative new markets, giving such work considerable economic and political salience. A key task involves determining the nature of the relationship between the device and the body in which it is located, and how enmeshed they prove to be with each other. Historically, medical devices have been conceptualized as materially circumscribed mechanisms that are inserted within the body to institute repair or enhancement at localized sites. In this sense, they were distinguishable from medicinal products designed to diffuse and operate systemically. Regulators have relied on these conceptions to triage regenerative devices, thus setting the trajectory of their path through the landscape of regulation and clinical trials.

The development of complex and much livelier regenerative assemblages such as Medtronic's combinatorial products *Infuse*™ and *Amplify*™ collapse these ontological distinctions by creating *devices that are systemic* in action and which become, in time, constitutive of the fragile humans in which they seed. An inability or unwillingness to recognize how such assemblages act to blur the boundaries between device and corporeality has resulted in an active disavowal of the implications of approving devices that enact the cyborg in real but wholly unanticipated ways. The risks to human subjects that arise when lively assemblages exceed their sites and mode of actions and go on to fully inhabit the architecture of the human body in ways that, due to their suffusive action and

imbrication, prove impossible to reverse, have yet to be fully acknowledged. Something that this case effectively highlights is the need for those who mobilize key edicts of human rights law as their raison d'etre to reflect on how the referents of those frameworks (in this case human beings) are being essentially re-made by their actions, and with what effects.

Insisting on the maintenance of a notional separation between body and technology in such cases works against Medtronic's patients and the FDA's charges in other, equally troubling, ways. Unwilling to accept that the cyborg bodies of their creation behave, predictably, in disturbingly more-than-human ways, Medtronic and its defense lawyers have sought to argue that it is the vagaries of the humans themselves and their unpredictable bodily responses that have invoked their "excessive" responses to the device. Causation in these cases, they argue, cannot be understood without this concept of "response," which remains highly individuated, thus providing grounds for the dissolution of many compensatory claims. The heterogeneity of the human condition—the very nature of what it is to be human—has been called into service to nullify appeals for fundamental human rights—rights to quality of life and basic standards of medical care, an irony indeed.

As the technical recrafting and regeneration of the human form continues, the work of holding apart what Sharon (2012:10) calls "supplemental and originary prostheticity" of the seemingly separate identities of the cyborg (the human and the technological) will become increasingly difficult to sustain. Fully imbricated rather than simply sutured into the corporeal fabric of the human form, these regenerative technologies can and will instantiate new renderings of the human form and inevitably spark fresh debates about what is to be human and about how the construct of "human" rights can be maintained and protected in this rapidly evolving, inherently transgressive, more-than-human world.

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Bronwyn Parry was trained as an economic and cultural geographer and is now Professor of Global Health and Social Medicine at King's College London. The author would like to thank her colleagues for the invitation to attend the very stimulating conference *New Technologies and Developments in the Biosciences and the New Frontiers of Human Rights* held at Durham University and funded by the Institute for Advanced Studies at Durham University, SLSA, Durham Law School and the Anthropology Department at Durham, which gave rise to this paper. She would also like to thank Noa Vaisman for her intellectual input and patience and the reviewers for their generous comments and assistance in refining this paper.

Bibliography

Bennett, Jane. *Vibrant matter: A political ecology of things*. Duke University Press, (2009).

Besmer, K. 2012. ‘‘Embodying a Translation Technology: The Cochlear Implant and Cyborg Intentionality.’’ Techné 16. No. 3: 296-316.

Carragee, Eugene J., Eric L. Hurwitz, and Bradley K. Weiner. "A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned." *The Spine Journal* 11, no. 6 (2011): 471-491.

Engelmeier, Robert. “The history and development of posterior denture teeth—introduction, part I” *The Journal of Prosthodontics* 12 (2003) 219 –226

Epstein, Nelly. “Complications due to the use of BMP/INFUSE in spine surgery: The evidence continues to mount.” *Surgical Neurology International*. 4, No Supp 5. S343-S352.

Finch, Jacqueline *et al*. "Biomechanical assessment of two artificial big toe restorations from ancient Egypt and their significance to the history of prosthetics." *Journal of Prosthetics and Orthotics* 24, No. 4 (2012) 181-191.

Fukuyama, Francis. "Our posthuman future." *New York: Farrar, Straus and Giroux* (2002)

Gibson, William. "Neuromancer. 1984." *New York: Ace* (1995).

Gottweis, Herbert, Brian Salter, and Cathy Waldby. *The global politics of human embryonic stem cell science: regenerative medicine in transition*. Springer, (2009).

Grubb, Andrew, Judith Laing, Jean McHale, and Ian Kennedy. *Principles of medical law*. Oxford University Press, (2010).

Gruen, L. "Attending to Nature: Empathetic Engagement with the More than Human World." *Ethics & the Environment*, 14, no. 2 (2009): 23-38.

Haraway, Donna. "A cyborg manifesto: science, technology, and socialist-feminism in the late twentieth century." *Simians, cyborgs and women: the reinvention of nature* (1991): 149-82.

Harris, John. "Taking the “human” out of human rights." *Cambridge Quarterly of Healthcare Ethics* 20, no. 01 (2011): 9-20.

Ilardi, Vincent. "Renaissance vision from spectacles to telescopes." In *Frontiers in Optics*, p. FWW7. Optical Society of America, (2004).

Jain, S. Lochlann. *Injury: The politics of product design and safety law in the United States*. Princeton University Press, (2006).

Latour, Bruno. "Body, Cyborgs and the Politics of Incarnation." In *The Body* Darwin College Lectures, edited by Sean Sweeney and Ian Hodder, Cambridge: University of Cambridge Press, (2002).

Lezaun, Javier. "The pragmatic sanction of materials: Notes for an ethnography of legal substances." *Journal of Law and Society* 39, no. 1 (2012): 20-38.

Lo, Bernard, and Lindsay Parham. “Ethical Issues in Stem Cell Research.” *Endocrine Reviews* 30, no. 3 (2009): 204–213.

Lorimer, Jamie. "Posthumanism/posthumanistic geographies." *International Encyclopedia of Human Geography* 8 (2009): 344-354.

Mason, Chris, and Peter Dunnill. "A brief definition of regenerative medicine." *Regenerative medicine* 3, no. 1 (2008): 1-6.

Mauras, Nelly, and Morey W. Haymond. "Metabolic effects of recombinant human insulin-like growth factor-I in humans: comparison with recombinant human growth hormone." *Pediatric Nephrology* 10, no. 3 (1996): 318-323.

Maher, Brendan. "How to build a heart." *Nature* 499.7456 (2013): 20.

Moore, Peter. *Blood and Justice: The 17 Century Parisian Doctor Who Made Blood Transfusion History*. John Wiley & Sons, (2003).

Nedelsky, Jennifer. *Law's relations: A relational theory of self, autonomy, and law*. Oxford University Press, (2011).

Oudshoorn, N. ‘‘Sustaining Cyborgs: Sensing and Tuning Agencies of Pacemakers and Implantable Cardioverter Defibrillators.’’ Social Studies of Science 45 no 1. (2015): 56-76.

Pashuck, E. Thomas, and Molly M. Stevens. "Designing regenerative biomaterial therapies for the clinic." *Science Translational Medicine* 4, no. 160 (2012): 160sr4-160sr4. 1-12

Riew, K. Daniel, and Eugene J. Carragee. "Commentary: Despite reports of catastrophic complications, why recombinant human bone morphogenetic protein-2 should be available for use in anterior cervical spine surgery." *The Spine Journal* 12, no. 10 (2012): 900-901.

Robertson, J. "Embryo Stem Cell Research: Ten Years Of Controversy.” *Journal of Law, Medicine & Ethics* no. 38. 2 (2010): 191–203.

Sharon, Tamar. "A Cartography of the Posthuman: Humanist, Non-Humanist and Mediated Perspectives on Emerging Biotechnologies." *Krisis* 2 (2012): 4-19.

Shaz, Beth H. "Blood work: a tale of medicine and murder in the scientific revolution." *Anesthesia & Analgesia* 116, no. 3 (2013): 740.

Simmonds, Mark C., et al. "Safety and Effectiveness of Recombinant Human Bone Morphogenetic Protein-2 for Spinal Fusion A Meta-analysis of Individual-Participant Data." *Annals of Internal Medicine* 158, No.12 (2013): 877-889;

Sobchack, V. 2006. ‘‘A Leg to Stand On: On Prosthetics, Metaphor, and Materiality.’’ In The Prosthetic Impulse: From a Posthuman Present to a Biocultural Future, edited by M. Smith and J. Morra, 17-41. Cambridge, MA: The MIT Press.

Sproull R. A history of porcelain dentistry. *Bulletin of the History of Dentistry* 1 no. 3 (1978) 10-26

Vaisman, Noa. "Relational Human Rights: Shed-DNA and the Identification of the 'Living Disappeared' in Argentina." *Journal of Law and Society* 41, no. 3 (2014): 391-415.

Van Den Eede, Yoni. "Where is the Human? Beyond the enhancement debate" *Science, Technology and Human Values* 40 (1) (2015): 149-62.

Whatmore, Sarah. "Materialist returns: practising cultural geography in and for a more-than-human world." *Cultural Geographies* 13, no. 4 (2006): 600-609.

Whitaker, M. J., R. A. Quirk, S. M. Howdle, and K. M. Shakesheff. "Growth factor release from tissue engineering scaffolds." *Journal of Pharmacy and Pharmacology* 53 (2001): 1427-1437.